National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome

AIDS VACCINE RESEARCH WORKING GROUP

Workshop on Design of HIV-1 Envelope Immunogens To Induce Broadly Neutralizing Antibodies

May 25-26, 2005
6700-B Rockledge Drive, Bethesda, MD

WORKSHOP SUMMARY

The AIDS Vaccine Research Working Group (AVRWG) met in public session on May 25 and 26, 2005, in Conference Room 1205 of 6700-B Rockledge, Drive, Bethesda, MD.

AVRWG members present: Barton Haynes (chair), James Bradac (executive secretary), Susan Buchbinder, Scott Hammer, Eric Hunter, Bette Korber, Steven Wakefield, Ian Wilson, Debrorah Birx (ex officio), Alan Greenberg (ex officio), Karen Goldenthal (ex officio), Gary Nabel (ex officio).

NIH personnel participating:

- Peggy Johnston, Director, Vaccine and Prevention Research Program (VPRP), Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID);
- Michael Pensiero, Preclinical Research and Development Branch (PRDB), NIAID;
- Stuart Shapiro, PRDB, NIAID.

Workshop presenters:

- Carole Bewley, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH;
- Marjorie Robert-Guroff, Basic Research Laboratory, National Cancer Institute (NCI);
- Richard Wyatt, Chief, Structural Virology Section, Vaccine Research Center, NIH.
- Anthony DeVico, Institute of Human Virology, University of Maryland Biotechnology Institute;
- Gail Ferstandig-Arnold, Center for Advanced Biotechnology and Medicine, Robert Wood Johnson Medical School, Rutgers University;
- Stephen Harrison, Department of Biochemistry and Molecular Biology, Harvard University;
- David Montefiore, Central Immunology Laboratory, Duke University Medical Center;
- William Olson, Progenics Pharmaceuticals;
- Indresh Srivastava, Chiron Corporation;
- Xinzhen Yang, Department of Pathology, Harvard Medical School.

Opening Remarks

Dr. Haynes welcomed participants and announced that the next AVRWG would be held on the afternoon of 6 Sep 2005, in conjunction with the AIDS Vaccine 2005 meeting in Montreal. An agenda will follow; one possible topic is the Gates-funded Global HIV Vaccine Enterprise. He also noted that today's meeting has drawn together many of the worlds leading experts on envelope immunogens.

Interpreting NAb results, neutralization assays, and standardized viral isolate panels

Dr. Montefiori reported that there has been considerable progress in measuring neutralizing antibodies (NAbs), but problems remain in generating and identifying candidate immunogens. The current gold standard is the peripheral blood mononuclear cell (PBMC) assay, which however is slow, expensive, coarse, and difficult to validate. The next generation of HIV neutralization assays must be sensitive, quantitative, reproducible, and high-throughput, optimized and validated to meet GLP standards for human clinical trials, and employ reagents that are standardized.

One promising new assay is based on TZM-b1 cell line (also called JC53-b1), a molecularly cloned envelope pseudovirus that expresses CD4, CXCR4 and CCR5 and contains Tat-inducible luciferase and beta-galactosidase reporter genes. This assay is faster (two days) and more precise (can measure 50-percent neutralization), and it has recently been optimized and validated. In comparative trials, TZM-b1 proved to be more sensitive than PBMC and other assays against a full range of HIV strains. What we need next are standardized reference reagents, including a standard panel of "real-world" HIV-1 reference strains for standardized assessments of vaccine-elicited neutralizing antibodies.

A workshop held at Duke University on January 6, 2005, sought consensus on the design and use of such reference strains. The criteria developed by the panel favored recently collected samples from early or acute stages of all six major clades, with a range of neutralizing phenotypes and nonreplicating pseudoviruses. The panel recommended that work begin immediately, using a tiered approach that would eventually grow to include 44 strains of HIV. Scientific issues that need to be addressed include the effects of genetic drift, the phenotype of acutely transmitted isolates, comparability of pseudoviruses as target cells, and the threshold bar for meaningful neutralization.

In response to questions, Dr. Montefiori added that PBMC-derived virus has shown diminished neutralization sensitivity, but efforts continue to improve that assay. Pseudoviruses are increasingly similar but show infection much faster and more sensitively. Cell density can be a problem – you can have too many cells. There are large differences in relative expression of CCR5 coreceptors in the two cell lines. [Li M, Gao F, Mascola JR, Stamatatos L, Polonis VR, Koutsoukos M, Voss G, Goepfert P, Gilbert P, Greene KM, Bilska M, Kothe DL, Salazar-Gonzalez JF, Wei X, Decker JM, Hahn BH, Montefiori DC. **Human immunodeficiency virus**

type 1 env clones from acute and early subtype B infections for standardized assessments of vaccine-elicited neutralizing antibodies. J Virol. 2005 Aug;79(16):10108-25]

Immunogenicity of a soluble trimeric envelope protein containing a partial deletion of the V2 loop

Dr. Srivastava described efforts by Chiron to evaluate the immunogenicity of modified envelope proteins, including monomer and trimer forms of gp140 from HIV subtype B SF162 with and without deletion of the V1 and V2 loops. Molecular tests showed that both trimers bind to CD4, and tests in macaques showed that they induced high virus inhibition. Further work in rabbits showed that VEE/SIN prime and protein boost produced the highest antibody titers, with significant reductions in viral load on challenge.

Dr. Robert-Guroff described current work, which involves adenovirus prime and protein boost. Preliminary results suggest that replication-competent adenovirus produces greater protection against the A, B, C, and E clades of HIV. Work also continues to identify effective adjuvants; unmethylated cytidine-guanosine dinucleotides (CpG) in particular look promising as a prime for protein boost, producing higher antibody titers and a broader neutralizing response against B clade strains.

In response to questions, the presenters agreed that priming appears to be very important, even if it is not perfectly matched to the protein boost. In some cases there is a high antibody titer but no breadth of neutralizing activity. It might be interesting to prime with one strain and then boost with another, or prime with adenovirus and then boost with both CpG and proteins. Results in chimpanzees are antibody response only; these animals are too valuable to challenge. Researchers would like to do more experiments with mismatched pairs. Participants suggested repeating the experiment to measure binding response, as well as neutralizing, or conducting PBMC assay after the pseudovirus assay. Side-by-side trials might lead to new conclusions about the best combination of prime and boost.

Studies of two novel vaccine designs based on HIV-1 envelope glycoproteins

Dr. Yang presented the results of animal studies showing that the antibody responses in rabbits immunized with gp120 monomer are largely against the outer domain (OD1) of the gp120 molecule. By creating independent OD1 proteins, however, investigators were able to determine that OD1-induced antibodies are non-neutralizing; neutralizing responses are produced by gp120-specific antibodies, not OD1-specific antibodies. Similarly, antibody responses in rabbits immunized with soluble gp140 trimer are not targeted toward the gp120 outer domain. On the contrary, soluble gp140 trimers induce strong trimer-specific responses that are broader and more strongly neutralizing than those induced by gp120 monomers. This improved antibody profile makes the gp140 trimer design a useful step toward an HIV vaccine candidate, but further improvements are still needed.

Questions from the participants had to do with whether neutralizing antibodies were absorbed, and whether non-neutralizing antibodies were binding to the trimer. Yang shared their concerns about interpreting results from HIV-positive sera, since it is difficult to know what is binding with what. Future work will focus on the mechanism of binding and the role of carbohydrates: cleavage appears to play an important role in antigenicity, as do disulfide particles, so investigators will try to generate a "cleaner, tighter" trimer. In addition, the binding response occurs in different regions of the human and rabbit molecules. Interest in gp120 is waning, but it may still be useful as a boost if investigators are able to achieve better standardization and purification at manufacturing volumes.

Disulfide-stabilized HIV-1 envelope trimers

Dr. Olson described efforts to stabilize the weak noncovalent association between gp120 and gp41 by introducing sulfide bonds between the two components to produce a stabilized SOSIP gp140 trimer. (Deleting the V1 and V2 loops from gp120 can also stabilize the trimer.) In rabbits, SOSIP gp140 mimics native envelope protein, inducing antibodies to both gp120 and gp41, including CD4 epitopes. Membrane-bound SOSIP gp140 gives the best prime, but DNA prime followed by SOSIP gp140 boost generates a stronger and more durable response, and there is robust neutralization in both pseudovirus and PBMC assays. Ongoing studies will include head-to-head comparisons of gp120 and SOSIP gp140 boost, with and without DNA boost, with further studies in summer 2005 leading to a go/no-go decision on one more related constructs. Current evidence suggests that SOSIP gp140 trimers mimic the native conformation and may represent an improvement over momeric gp120 in eliciting neutralizing antibodies against HIV isolates.

In response to questions, Olson said that the rate-limiting step in this process was the ability to synthesize and screen stable trimers. Investigators have not yet screened trimers from which the V1 and V2 loops were deleted, although they plan to do so in future. V3 deletion depletes neutralization against some isolates but not others. The compounds have not yet been tested against clade A pseudoviruses.

Covalent trimers of the internal N-terminal trimeric coiled-coil of gp41

Dr. Bewley presented information on the effects of gp41 analogs as inhibitors and immunogens. NCCG-gp41, a chimeric protein featuring an exposed trimeric coiled-coil comprising the N-terminal helices of the gp41 ectodomain, has proven to be highly immunogenic and highly inhibitory of the HIV-1 envelope-mediated fusion. Investigators have gone on to identify several more potent variants, which may have potential as therapeutic agents. Purification yields two pools of antibodies, one tightly binding and the other weakly binding. There are no apparent differences between the two antibodies, but the tightly binding antibodies are better inhibitors of fusion. Work in progress is designed to identify additional N-trimer-specific antibodies, determine whether then are neutralizing, and raise anti-N-trimer antibodies in Mage rabbits. More antibody will be needed to address questions such as where the trimer binds.

Design and identification of human rhinovirus:HIV-1 gp41 ELDKWA chimeras that elicit cross-neutralizing antibody responses

Dr. Ferstandig-Arnold explained that human rhinovirus (HRV) is a relatively mild virus that nevertheless stimulates a robust immune response, making it a possible vector for a live-virus vaccine. Researchers have created chimeras of HRV that includes the ELDKWA epitope from gp41 surface loops, a component of the fusion machinery that is highly conserved across HIV isolates. In the chimeras, the ELDKWA successfully elicits 2F5, a highly neutralizing antibody that inhibits fusion. At present only 50 percent of chimeras express 2F5, but investigators hope to improve this rate.

Based on this result, investigators compiled a library of about 10^7 variants of the chimera, some randomized but others expressing HIV sequences, and tested them to see how well they were neutralized by 2F5. A total of 20 chimera were tested in guinea pigs, and 12 produced NAbs against one or more clades of HIV-1; all were mixtures of HIV and random residues. The best worked against 6 of the 7 isolates being tested. One or two peptide boosts were found to improve neutralization in some isolates, but 2F5 activity varied among sera. The next step will be to study the best candidates to discover the three-dimensional correlates of immunogenicity.

In response to questions, Dr. Ferstandig-Arnold said that investigators have also tried different combinations of the best chimera. Investigators used murine leukemia virus (MLV) as a negative control, but it does not work as well in guinea pigs as it does in mice, and they will use a different control in future. Results against the ALDKWA variant were stronger than expected, possibly because the Ab targets the DKW core sequence. Plans are underway to test the DSW substitution. Peptide boost is keyhole limpet hemocyanin (KLH). The size of the chimeric loop is variable, but the goal is a stable conformation that is flexible in interaction. Investigators believe that anything that survives the library approach will be stable.

Analysis of HIV-1 envelope glycoproteins for immunogen design to elicit broadly neutralizing antibodies

Dr. Wyatt noted that gp120 and gp41 are the only viral protein targets for NAbs, yet it remains difficult to elicit broad and potent NAbs during natural infection. This is because gp41 is well occluded in the functional spike, while the conserved elements of gp120 are shielded by carbohydrate and the exposed elements are highly variable in conformation. However, a few HIV-infected patients do have broadly neutralizing Abs in their sera (e.g., 2F5, 4E10,447D, 2G12, IgDb12). Investigators don't currently know whether these Abs target gp120 or gp41, which is why both proteins are being pursued in vaccine design, using a combination of biochemistry and biophysics.

The target for one effort is to stabilize gp120 at the binding site with CD4 by using four cysteines to bridge and fill the gaps in the bound conformation. However, some "pocket-filling formations" (e.g., PF2) variants don't stabilize yet exhibit increased neutralization, while others won't fold and therefore aren't bound. The second target is the 4E10 structure on the gp41

membrane proximal region (MPR), which is highly conserved across HIV isolates. Structural studies have shown that the CDRH3 loop in the MPR is highly hydrophobic, and that the 2F5-bound conformation of gp41 assumes a unique extended conformation that occludes one face of the gp41 epitope, which remains bound to the membrane. Taken together, these discoveries may allow investigators to design epitope mimetics that elicit 2F5-like Abs. Some investigators are pursuing this lead genetically, by stabilizing DNA expression; others are pursuing it synthetically, by trying to stabilize the epitope.

In answer to questions, Dr. Wyatt said that the structural problem appears to be functional rather than steric. Binding is antigen-driven, so agents are chosen for affinity to gp160. Testing will include MPR prime and p160 boost.

Immunogens based on constrained gp120

Dr. DeVico described investigations of CD4-liganded gp120 Abs, whose existence has been known for 10 or 15 years. It is well known that some Abs to CD4-induced (CD4i) gp120 epitopes are broadly neutralizing; the question is whether these Abs are worth pursuing in the search for HIV vaccines. The best strategy may be to move them into primates. Previous studies have suggested that coreceptor density and entry kinetics might influence the neutralizing capacity of CD4i Abs. Several single-chain gp120-CD4 immunogens are already in Phase 1, and one has progressed to pre-IND.

Investigators are now conducting a "Complex II" pilot study to determine whether single-chain and/or cross-linked complexes will provide protective immunity in a rhesus macaque model when mucosally challenged with R5 virus. Four different immunogens and controls will be used in a total of 20 animals followed for 5 years. Preliminary data show that NAbs were raised in three of the four experimental arms, but titers were modest and on challenge only one immunogen (containing epitopes from gp120 and rhesus CD4) reduced viral load in sera and tissues. Investigators conclude from this that elements of the vaccine other than the immunogens were responsible for suppressing infection; they now plan new experiments to optimize the protocol and boost the immune response.

In response to questions, Dr. Wyatt said that "broadly neutralizing" means effective against two isolates. There is no clear evidence of secondary response with the vaccine as the prime immunization. Animals develop Abs to both human and rhesus CD4; future protocols will have CD4 controls. There is no response in mice to the lead candidate (FCSL, a combination of gp120 and CD4 epitopes). Participants suggested that Wyatt send sera to George Shaw at UAB for assays to detect Abs. They also suggested that the time may have come to challenge these candidates with simian immunodeficiency virus (SIV) rather than SHIV. Wyatt agreed – he wouldn't expect envelope-specific Abs to neutralize SIV, but the preliminary data can't be based solely on CD4 epitopes.

VRC multiclade vaccine: Env-neutralizing Abs and next-generation vectors

Dr. Nabel suggested that, while envelope proteins can drive effective cellular immunity in animals and humans, a successful HIV vaccine must also elicit broadly neutralizing Abs to the maximal extent possible. First-generation vectors do elicit Ab response, but they require further improvement. For example, experience has shown that a combination of Env from different clades will induce a broader and stronger NAb response than Env from a single clade.

Consequently, the NIH Vaccine Research Center (VRC) has developed a prototype DNA vaccine (VRC004) that combines elements of the envelope protein gp145 from HIV-1 clades A, B and C, along with Gag, Pol and Neg epitopes from clade B. This combination elicits a strong and specific Ab response that is strongly dose-dependent. Further refinements include deleting the V_1 and V_2 loops from the clade A protein, which improves the V_3-mediated neutralization against clade B, and shortening the V_3 loop from clade C, which further improves and broadens the neutralizing response by eliminating a number of mutations in the stem of the V_3 loop.

At present it is not clear whether broadly neutralizing Ab immunogens can best be designed by structural or genetic approaches, or both. More importantly, it is unclear whether the better strategy is to target epitopes that are conserved but may be inaccessible (e.g., CD4, CD4i complexes, MPR region), or to target more exposed regions that are variable but may have some highly conserved subdomains.

In answer to questions, Dr. Nabel added that Env from different clades have consistent patterns of reactivity, with clade A being the most immunogenetic. Experience has shown that the location of the glycolysation site is not as important as the presence of the V_1 and V_2 loops.

Polyspecific reactivity of broadly reactive neutralizing antibodies

Dr. Haynes described work at the Duke Human Vaccine Institute to isolate and evaluate the Abs 2F5 and 4E10, which are robustly and broadly neutralizing against epitopes in the gp41 MPR ectodomain. Research has shown Abs like 2F5 and 4E10, which have with long, hydrophobic CDR3 loops, are often counterselected in the late stages of B-cell development through receptor editing and clonal deletion. This may be because MPR-neutralizing Abs mimic autoantigens.

To discover why they are deleted, researchers analyzed a total of 35 HIV-relevant Abs for reactivity with a range of human autoantigens. Thirty-one were negative in most tests, but 4 Abs reacted with three or more classes of autoantigens, including 4E10 (which binds strongly to cardiolipin [CL] in lamellar form) and 2F5 (which has a lower affinity for CL and prefers the hexagonal phase). CL is a phospholipid found in patients with lupus, where it poses a risk of thrombosis and miscarriage. Anti-CL Abs have been reported in up to 45 percent of HIV-1 patients, but it is rare for lupus patients to become infected with HIV-1. Further investigation showed that the anti-CL Abs IS4 and IS6 binds to gp140 envelope protein, but not to gp120, and that neither anti-CL Ab neutralizes HIV-1 in the absence of gp160 hyperactivation. Unanswered questions that will drive future research include whether anti-CL Abs are reactive with gp41 MPR, whether autoimmune patients produce MPR Abs after HIV-1 infection, whether those Abs are really deleted during immunization, and whether it is possible to “break tolerance”

to MPR and produce neutralizing Abs. The latter question will probably require work on adjuvants to break tolerance to autoantigens, and there will also be a need for structural studies to design modified Env immunogens that either break tolerance or recruit monospecific B2 cells to respond to gp41 MPR.

In response to questions, Dr. Haynes said that differences in 4E10 binding might be due to different phospholipid levels in tissues; this postulate could be tested through non-HIV binding tests against antiphospholipid disease and lupus. In the case of 2F5, the response that is not blocked is nonspecific or polyspecific; it may be the same for all clonal deletion – high-affinity Abs are deleted but low-affinity Abs are retained. On the other hand, it appears that gp160 can drive a heterologous response in anergic B cells. It would be a good idea to do a knockout mutation to eliminate the long hydrophobic loop and determine the effect on binding. Mice would be a good model, since they have a shorter CDR3 loop in the first place. 2E5 has a half-life of 5 days, 4E12 about 10 days, and their peptide bindings are variable; it would be desirable to do functional tests. There is no evidence that breaking tolerance will require inducing autoimmune disease, nor is there any evidence of autoimmune response in animals or humans who receive the vaccine.

What can we learn about Env immunogenicity by comparing the unliganded and receptor-bound conformations of gp120?

Dr. Harrison described some of the conformational changes that occur as HIV-1 envelope proteins interact with the cell membrane to enable viral RNA entry. During HIV-1 infection, gp120 unbinds from gp41 and several elements shift independently as it "unravels" to become a fusion pore. Ordinarily, the inner domain of gp120, which connects to the "stalk," tends to flicker between different conformations. CD4 "fixes" this conformation, but the CD4 receptor is hidden in the liganded state. Freed from gp120, gp41 undergoes changes in its own hairpin domains and later forms another fusion pore.

In response to questions, Harrison explained that CD4 fixes the shape assumed by gp120 but does not determine it; increasing the energy of the conformation would decrease the likelihood of binding. On the other hand, gp120 experiences "an array of entropies" as it flickers between conformations, and Abs could pull it into intermediate confirmations that prevent binding. It seems logical that resistance occurs because gp120 has been induced to spend more time in unreceptive confirmations. This could explain differences in susceptibility and levels of neutralization – the Env-Ab conformation expresses a range of equilibrium, rather than a yes-or-no, all-or-nothing dichotomy.

Structural basis for neutralization of HIV-1

Dr. Wilson posited that broadly neutralizing Abs to HIV-1, while rare, do exist; the challenge is to characterize them and combine them into an effective vaccine. It is well know, for example, that 2G12 binds to gp120, and that the crystal structure of 2G12 includes a domain-swapped dimer that gives it a high avidity for binding with a unique carbohydrate antigen on the surface of gp120. Smaller pieces of 2G12 might be used as an alternative antigens, and indeed investigators have identified one epitope mimic that is 46 times more effective than the natural oligomannose cluster on 2G12. This raises hope for developing a carbohydrate-based vaccine.

Similarly, 4E10 has an affinity for a helical peptide (KGND) on the hydrophobic face of gp41. Knowing the requirements for this affinity, investigators have been able to identify a number of gp41 peptides that might be used to induce NAbs, and they are now screening these peptides for affinity, helicity and solubility. A refined list of candidate peptides will be communicated to colleagues for further testing. Because several other HIV-1 Abs also use long CDR3 loops, this "retrovaccinology" approach may be useful in additional antigens.

In response to questions, Dr. Wilson explained that many antibodies might bind to Env without neutralizing because they don't hit the right face(s) of the target protein. In many cases, the neutralizing effect is due to steric interference rather than binding. Long CDR3 loops are fairly uncommon structures in other Abs; canyons are more common than pockets. Ultimately, all candidate antigens will need to be tested in an neutralization screen and won't go forward unless they block infection.

An unrelated monoclonal antibody neutralizes by binding to an artificial epitope engineered by the gp120 V_4 region of HIV-1 envelope glycoproteins

Dr. Yang noted that Abs bind to many different regions of gp120, but he posited that those that achieve neutralization do so by one of only three mechanisms:

14. Direct competition for receptors;
15. Disruption of structural changes; or
16. Steric hindrance.

To determine if steric hindrance alone is sufficient to neutralize HIV-1, researchers designed an Ab that binds to a region that is not involved in important functions of the protein. The V_4 loop seemed promising, because it is highly variable, highly exposed, has no secondary structure, no known function or overlap, and no known mutation in V_4 sequence had any effect on gp120 function. They inserted a FLAG tag on the V_4 loop as an artificial epitope for Ab binding and then demonstrated that the M2 Ab specifically neutralized gp160 with a FLAG tag on the V_4 loop. Since it could also be demonstrated that M2 doesn't compete for receptor sites or disrupt structural changes, this effect must be steric. This demonstrates that steric hindrance alone is sufficient to cause neutralization. This provides a novel experimental system to study the mechanisms of Ab-mediated neutralization.

In response to questions, Dr. Yang added that Env has many different regions, and he would not expect any given Ab to be polyclonal in effect. He could not explain why so many Abs bind to Env without neutralizing, except to suggest that binding affinity may play a role. M2 does not have a high affinity for FLAG. It is possible that the V_4 loop does have a function that remains unknown.

Discussion and Recommendations

Dr. Johnston reported that the budget for vaccine development is leveling off, and that relatively little of that budget is discretionary (most of it goes to centers and contracts). On the other hand, DAIDS funds relatively few unsolicited R01 proposals in vaccine research, typically two or three, although there were six in the most recent cycle. This was because the proposal were better, not because there were more of them. What DAIDS needs from AVRWG is broad guidance on (1) what's most important in AIDS vaccine development and (2) where does DAIDS need to intervene with additional resources (staff or money). Dr. Tramont added that vaccine research has done well in the past because of input from AVRWG, and DAIDS welcomes challenges and questions on research priorities.

Dr. Bradac outlined the seven major approaches to AIDS vaccine research that are inherent in the presentations to this workshop:

1. Multimeric Env immunogens;
2. Env mutations to stabilize or expose conserved epitopes;
3. Transitional state proteins that mimic entry intermediates;
4. Stabilized trimeric protein (e.g., SOSIP);
5. Expression of native protein on virus-like proteins;
6. Mimic carbohydrate structures (e.g., 2G12 epitope).
7. Miscellaneous approaches that don't fit any of the above.

In addition, DAIDS Basic Science Program has several projects relevant to crystalline and protein structure, mechanisms of neutralization, and adjuvants. The Gates Foundation has issued RFPs for its Global HIV Vaccine Enterprise that involve not only broadly immunizing Abs but also standard reagents and assays. The International AIDS Vaccine Initiative (IAVI) is also expanding is activities in this area. It is the hope of DAIDS that these activities will grow the pool of funding for vaccine research and bring new resources to the development side of the equation, which NIH and DAIDS have not and cannot push. Interaction and coordination among these efforts will be vital.

Participants agreed that high-profile failures might such resources out of the field and create disincentives for further attempts. However, Gates in particular acknowledges that the front end is the limiting stage at present; they will shift resources toward advanced development as the field matures. Several participants suggested that DAIDS makes a huge contribution by sponsoring cross-cutting scientific meetings, like the present workshop, where DAIDS grantees and contractors can talk to one another informally. This requires staff rather than money, and

DAIDS, like the rest of NIH, has trouble getting additional FTEs; the recent conflict of interest blowup has added new complications.

Several participants suggested that the field has gotten too big for impromptu workshops, but that it would be useful to append vaccine research workshops to other large AIDS meetings, such as Keystone, AIDSVAC and CROI. These workshops should include opportunities for junior researchers to present posters and abstracts. Gates and IAVI might also be asked to sponsor workshops. Several participants stressed that these workshops should be small and informal, with adequate time at the end to identify and discuss important technical questions. Webcasting might be another way to build awareness and outreach.

Several participants suggested that it would be useful for someone to establish a clearinghouse for preclinical research on AIDS vaccines, similar to the one being set up for human data. Ideally, such a clearinghouse would link human and nonhuman results. However, several participants indicated that it was too soon assign priorities to the seven categories of vaccine research, or – while the trimer results are intriguing – to pick trimers over gp120. Perhaps it would be useful to conduct comparative trials in rabbits and macaques before taking the next step, but the field is looking for dramatic improvements rather than incremental.

Plans for AVRWG Meeting at AIDS Vaccine 2005

The next meeting of AVRWG will be on September 6, 2005, from 2 to 6 p.m., in conjunction with the AIDS Vaccine 2005 meeting in Montreal. Possible agenda items include followup on the vectors workshop, followup on this antibody workshop, and (possibly) liability and indemnification of investigators on NIH-sponsored HIV-1 vaccine trials. Rick Klausner should be invited to discuss ways to foster communication and collaboration among sponsors. DAIDS will circulate an agenda a week or two ahead of the meeting, along with a few pages of "read-ahead" materials.

Review of DAIDS Vaccine Preclinical Portfolio

Dr. Bradac reported that DAIDS supported 15 Innovation Grants in FY 2005, plus 8 R01 grants in two cycles. Awards for HIVRAD and IPCAVD are pending, and CHAVI is in review. New initiatives in FY 2006 will include an RFP for Simian Vaccine Evaluation Units, a new program announcement in vaccine design, and expansion of CHAVI. DAIDS will hold a nonhuman primate meeting in the fall to review tests, results and grants.

Preclinical Vaccine Pipeline Update

Dr. Pensiero reported that DAIDS now supports 19 different contracts that investigators can use for novel vectors, assays, etc. A new Vaccine Development Resource Group will provide technical assessments of requests for access to those resources. A number of vaccines are moving into advanced testing, including three new products from Wyeth and two from Chiron, and a number of additional candidate vaccines will soon enter the pipeline. New partnerships

with DOD and CDC should provide some "pull" at the other end, but eventually the industrial partners will want to narrow the field in order to select candidate(s) for advance production.

Center for HIV/AIDS Vaccine Immunology (CHAVI)

Dr. Shapiro explained that when CHAVI awards are announced in early September, this initiative will have gone from concept to contracts in less than 12 months. Significantly, this is a center for vaccine *immunology*, not vaccine *development* – it will use new and sophisticated tools to search for the correlates and mechanisms of protection, with the goal of advancing the intelligent design of vaccines for AIDS.

In answer to questions, Shapiro added that CHAVI will use an iterative process, working from best guesses to seek the science to confirm and apply new knowledge. The program will be funded for seven years, with a budget of $14 million in year 1 growing to $50 million/yr. It will be a "virtual vaccine development center," working through cooperative agreements with NIAID, GHVE, IAVI, etc. to address the basic problems in vaccine development. Significantly, the budget contains no money for building or renovations. The most important goal in year 1 is to choose a strong director who will exert leadership in the field, fostering aggressive interaction through small grants to outside groups. By asking applicants to identify gaps and challenges, CHAVI has assembled the components of an innovative strategic plan, as well as catalyzing a number of collaborations that bode well for progress in this area.

The meeting adjourned at 11:50 a.m.